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Short Communication

Mosaic small supernumerary marker chromosome 1 at amniocentesis: Prenatal diagnosis, molecular genetic analysis and literature review

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ABSTRACT

We present prenatal diagnosis and molecular cytogenetic analysis of mosaic small supernumerary marker chromosome 1 [sSMC(1)]. We review the literature of sSMC(1) at amniocentesis and chromosome 1p21.1-p12 duplication syndrome. We discuss the genotype–phenotype correlation of the involved genes of *ALX3*, *RBM15*, *NTNG1*, *SLC25A24*, *GPSM2*, *TBX15* and *NOTCH2* in this case.

1. Introduction

A small supernumerary marker chromosome (sSMC) is a structurally abnormal chromosome that cannot be characterized by conventional banding techniques and has the size equal to or smaller than chromosome 20 (Liehr et al., 2004). Prenatally ascertained sSMCs occur in 0.075% of prenatal cases (Liehr, 2008; Liehr et al., 2004, 2009). The overall risk of phenotypic abnormalities in prenatally ascertained sSMCs has been estimated to be about 13% (Warburton, 1991). Crolla et al. (1998) suggested that the risk of phenotypic abnormalities in sSMCs derived from non-acrocentric autosomes is higher than that from acrocentric chromosomes (28% *vs.* 7%). Liehr and Weise (2007) suggested a 30% risk for an abnormal phenotype in prenatally ascertained sSMCs derived from non-acrocentric autosomes.

Chromosome 1-derived sSMC [sSMC(1)] has been reported in at least 75 cases, of which 52 cases (69.3%) had clinical findings and 23 cases (30.7%) had no clinical findings (Liehr, 2013). Very few prenatally ascertained sSMCs(1) have been investigated by comprehensive molecular cytogenetic techniques to identify the genetic component of the sSMC. Herein, we present our experience of prenatal diagnosis of mosaic sSMC(1) with molecular genetic analyses on uncultured amniocytes, and we review the literature.

Abbreviations: OMIM, Online Mendelian Inheritance in Man; sSMC, small supernumerary marker chromosome; aCGH, array comparative genomic hybridization; FISH, fluorescence *in situ* hybridization; del, deletion; der, derivative chromosome; r, ring chromosome; mar, marker chromosome; inv, inverted; dup, duplication; mat, maternal; UPD, uniparental disomy; AFP, α-fetoprotein; CNS, central nervous system; QF-PCR, quantitative fluorescent polymerase chain reaction; IUGR, intrauterine growth restriction; MCB, multicolor banding; SKY, spectral karyotyping; NT, nuchal translucency; VSD, ventricular septal defect; PDA, patent ductus arteriosus.

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2. Materials and methods

2.1. Clinical description

A 34-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 38 years old. Amniocentesis revealed a karyotype of 47, XY,+mar[10 colonies]/46,XY[11 colonies]. Among 21 colonies of cultured amniocytes, 10 colonies contained an sSMC, whereas the rest 11 colonies had a normal karyotype. Repeated amniocentesis at 20 weeks of gestation using aCGH on uncultured amniocytes confirmed that the sSMC originated from chromosome 1. She underwent fetal blood sampling and additional amniocentesis at 23 weeks of gestation. Fetal blood had a karyotype of 47,XY,+mar[8 cells]/46,XY[32 cells]. Cultured amniocytes had a karyotype of 47,XY,+mar[13 colonies]/46,XY[27 colonies] (Fig. 1). aCGH on uncultured amniocytes revealed a 15.63-Mb gene dosage increase at 1p21.1-p12 (Fig. 2). Interphase FISH analysis showed 51.7% (46/89) mosaicism for sSMC(1) in uncultured amniocytes (Fig. 3). The parental karyotypes were normal. Polymorphic DNA marker analysis excluded uniparental disomy (UPD) 1. Prenatal ultrasound findings were unremarkable. The parents elected to terminate the pregnancy. A 526-g fetus was delivered with hypotelorism, low-set ears, micrognathia, a bulbous nose with prominent nasal bridge, small mouth and clinodactyly of the hands. Postnatal cytogenetic analyses of extraembryonic tissues revealed a karyotype of 47,XY,+mar[19 cells]/46,XY[21 cells] in the umbilical cord and a karyotype of 47,XY,+mar [18 cells]/46,XY[22 cells] in the placenta.

2.2. aCGH

Whole-genome aCGH on uncultured amniocytes derived from 10 mL of amniotic fluid at repeated amniocentesis was performed using NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA). The NimbleGen ISCA Plus Cytogenetic Array has 630,000 probes and a median resolution of 15–20 kb across the entire genome according to the manufacturer's instruction.

2.3. Conventional cytogenetic analysis

Routine cytogenetic analysis by G-banding techniques at the 550 bands of resolution was performed. 20 mL of amniotic fluid was collected at repeated amniocentesis, and the sample was subjected to *in situ* amniocyte culture according to the standard cytogenetic protocol. Parental bloods, fetal blood, umbilical cord and placental tissues were collected, and the samples were subjected to culture according to the standard cytogenetic protocol.

2.4. Fish

Interphase FISH analysis on uncultured amniocytes was performed using a 1p11.2-specific probe RP11-115N23 (spectrum green, FITC) (121,227,660-121,379,066) [hg 19] according to the standard FISH protocol. Metaphase FISH analysis on cultured amniocytes was performed using the chromosome 1/5/19 α-satellite-specific gene probe (spectrum green, FITC), located at the homologous centromeres of chromosome 1 (D1Z7; 1p11.1-q11.1), chromosome 5 (D5Z2; 5p11.1-q11.1) and chromosome 19 (D19Z3; 19p11.1-q11.1), and chromosome 1 α-satellite-specific gene probe D1Z1 (1q12) (spectrum red).

3. Results

Whole-genome aCGH analysis on uncultured amniocytes detected a 15.63-Mb mosaic duplication at 1p21.1-p12, or arr [hg 19] 1p21.1p12 (104,907,786-120,533,755) × 2.7 (Fig. 2). The duplicated 1p21.1p12 region contains 236 genes including 106 OMIM genes. Interphase FISH analysis on uncultured amniocytes showed that among 89 interphase uncultured amniocytes, 46 had three 1p11.2-specific green signals, and 43 had two green signals, indicating 51.7% mosaicism for sSMC(1) in uncultured amniocytes (Fig. 3). Metaphase FISH analysis on cultured amniocytes showed that the marker chromosome contained D1Z7 (1p11.1-q11.1) but no D1Z1 (1q12) (Fig. 4). The marker chromosome was sSMC(1) or der(1)(:p21.1 → q11:).

4. Discussion

To date, at least 24 cases of prenatally ascertained sSMC(1) at amniocentesis have been reported (Anguiano et al., 2012; Bartsch et al., 2005; Constantinou et al., 2005; Cotter et al., 2005; Crolla et al., 1998; Fickelscher et al., 2007; Gruchy et al., 2008; Kaluzewski et al., 2007; Lefort et al., 2004; Li et al., 2000; Liehr, 2013; Liehr et al., 2010; Marle et al., 2013; Michalski et al., 1993; Rodríguez et al., 2005; Schneider et al., 2007, 2011; Spiegel et al., 2003; Tönnies et al., 2007; Wray et al.,

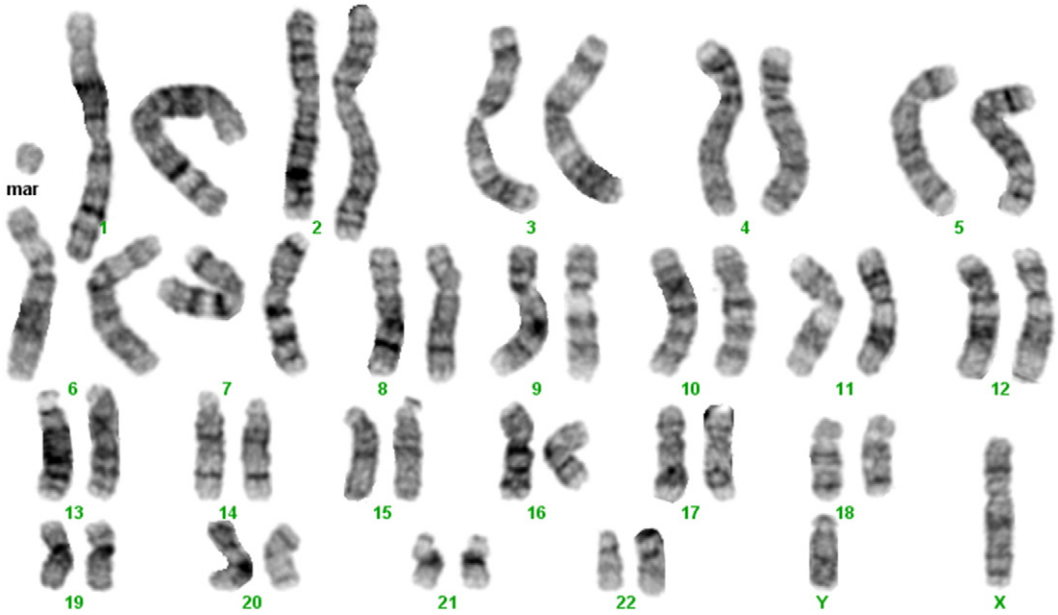

Fig. 1. A karyotype of 47,XY,+mar.